

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



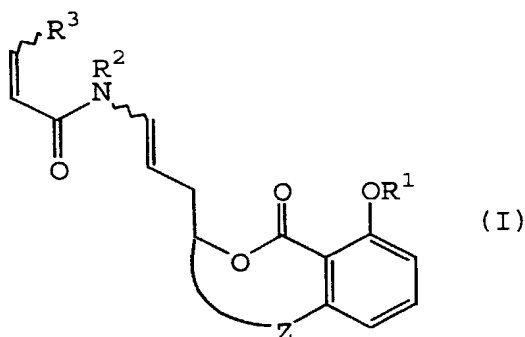
(43) International Publication Date
8 September 2000 (08.09.2000)

PCT

(10) International Publication Number
WO 00/51589 A3

- (51) International Patent Classification⁷: **A61K 31/365**,
A61P 35/00, 35/04, 15/08, 19/10
- (21) International Application Number: PCT/US00/05582
- (22) International Filing Date: 3 March 2000 (03.03.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
60/122,953 5 March 1999 (05.03.1999) US
60/169,564 8 December 1999 (08.12.1999) US
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- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- Published:
— With international search report.
- (88) Date of publication of the international search report:
12 July 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: VACUOLAR-TYPE (H⁺)-ATPase-INHIBITING COMPOUNDS, COMPOSITIONS, AND USES THEREOF



(57) Abstract: The present invention provides vacuolar-type (H⁺)-ATPase-inhibiting compounds, compositions thereof, and methods of using them to treat or prevent a condition treatable by the inhibition of a vacuolar-type (H⁺)-ATPase. The composition of the present invention comprises a compound of the present invention and a carrier. The method of the present invention includes administering a vacuolar-type (H⁺)-ATPase inhibiting-effective amount of a compound of the present invention. The compound of the present invention has formula (I) wherein R¹ and R² are H, saturated or unsaturated alkyl, aryl, R⁶CH₂-, R⁶CO-, or R⁶SO₂-, wherein R⁶ is H, saturated or unsaturated alkyl, or aryl; R³ is H, alkyl, aryl, an oxime, or an oxime methyl ether; the aromatic ring is unsubstituted or substituted; and Z is a contiguous linker comprising a chain of 0-10 atoms which, together with the five atoms beginning with the carbon of the aromatic ring in meta-relationship with OR¹ and ending

with the carbon directly attached to the alkyl oxygen of the lactone, integrally form a 5-17 membered ring; or a pharmaceutically acceptable salt, an ester, or a prodrug thereof.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/05582

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/365 A61P35/00 A61P35/04 A61P15/08 A61P19/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>GALINIS L DEBORAH ET AL: "Lobatamides A and B. Novel Cytotoxic Macrolides from the Tunicate Aplidium lobatum" JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 62, no. 26, 1997, pages 8968-8969, XP002111864 ISSN: 0022-3263 page 8968, left-hand column</p> <p style="text-align: center;">---</p> <p style="text-align: center;">-/--</p>	1,17,19, 35

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
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- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

8 December 2000

Date of mailing of the international search report

21/12/2000

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/05582

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>ERICKSON L ET AL: "Salicylhalamides A and B, Novel Cytotoxic Macrolides from the Marine Sponge Haliclona sp" JOURNAL OF ORGANIC CHEMISTRY, US, AMERICAN CHEMICAL SOCIETY. EASTON, vol. 62, no. 23, 1997, pages 8188-8192, XP002111863 ISSN: 0022-3263 page 8191, left-hand column; examples 1,2</p> <p>---</p>	1,17,19, 35
X	<p>WO 99 05136 A (PANNELL LEWIS ;BEUTLER JOHN A (US); BOYD MICHAEL R (US); ERICKSON) 4 February 1999 (1999-02-04) cited in the application claims 1,7,18</p> <p>---</p>	1,17,19, 35
X	<p>K. A. DEKKER ET AL : "Novel lactone compounds from Morterella verticillata that induce the human low density lipoprotein receptor gene: fermentation, isolation, structural elucidation and biological activities" JOURNAL OF ANTIBIOTICS., vol. 51, no. 1, 1998, pages 14-20, XP000971100 JAPAN ANTIBIOTICS RESEARCH ASSOCIATION. TOKYO., JP ISSN: 0021-8820 cited in the application page 14, left-hand column; figure 1</p> <p>---</p>	1,19
X	<p>JIN WOO KIM ET AL: "Oximidines I and II: Novel antitumor macrolides from Pseudomonas sp." JOURNAL OF ORGANIC CHEMISTRY., vol. 64, no. 1, 1999, pages 153-155, XP000971102 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 cited in the application page 153, left-hand column, line 1 - line 7; figure 1</p> <p>---</p>	1,17,19, 35
A	<p>KEN-ICHI SUZUMURA ET AL: "Structural elucidation of YM-75518, a novel antifungal antibiotic isolated from Pseudomonas sp.Q38009" TETRAHEDRON LETTERS, vol. 38, no. 43, 1997, pages 7573-7576, XP002154892 OXFORD GB figure 1</p> <p>-----</p>	1,17,19, 35

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-11,19-29

Present claims 1-11,19-29 relate to a method and composition defined by reference to the following term : vacuolar-type (H⁺)-ATPase. The use of this term in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the parts relating to the method and composition mentioned in the description at pages 20-21.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter. Personal Application No

PCT/US 00/05582

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9905136 A	04-02-1999	AU 8501598 A EP 1000053 A	16-02-1999 17-05-2000
